Clinical advances in musculoskeletal imaging: spondylodiscitis and pediatric oncology

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Chapter 5

CT-guided bone biopsies with indeterminate results in pediatric patients

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AJR American Journal of Roentgenology 2018;211:661-671

Abstract

Objective

To determine the frequency of indeterminate percutaneous computed tomography (CT)-guided bone biopsy results in a pediatric population, the subsequent management of the indeterminant biopsy result, and the factors associated with indeterminant biopsy result.

Materials and Methods

This retrospective study included 86 pediatric patients who underwent 89 CT-guided biopsies because of an unclear bone lesion in a tertiary referral center for bone tumors.

Results

There were 29/89 indeterminate CT-guided bone biopsy results (32.6%, 95% confidence interval [CI]: 23.7-42.9%]). Excluding 2 bone lesions whose nature remained uncertain, all other 27 bone lesions proved to be benign on follow-up (0%; 95% CI: 0-12.5%). Compared to patients with diagnostic CT-guided bone biopsies, patients with indeterminate biopsy results were significantly younger (median age of 14.0 vs. 18.0 years, *P*=0.0185), were more frequently female (72.4% vs. 41.7%, *P*=0.0007), and less frequently had bone lesion related symptoms. (62.1% vs. 88.3%, *P*=0.0094). Furthermore, bone lesions were significantly more frequently invisible at CT (24.1% vs. 1.7%, *P*=0.0021), more frequently had a sclerotic rim (40.9% vs. 18.6%, *P*=0.0477), less frequently showed cortical destruction (45.5% vs. 72.9%, *P*=0.0343), less frequently had an associated extraosseous soft tissue mass (4.5% vs. 32.2%, *P*=0.0094), were smaller (median diameter of 17.0 vs. 31.0 mm, *P*=0.0007), and the maximum biopsy sample length was significantly shorter (mean length of 10.9 vs. 17.8 mm, *P*=0.0003).

Conclusion

A non-diagnostic CT-guided biopsy result in a child with an unclear bone lesion suggests benignity. Several clinical and CT features of bone lesions are associated with indeterminate CT-guided bone biopsy results.

Introduction

Percutaneous computed tomography (CT)-guided biopsy is a well-established minimally invasive procedure for the evaluation of bone lesions in adults, with reported diagnostic yields exceeding 70% [1-3]. However, the use of CT-guided vs. direct open bone biopsy in children remains a topic of discussion, because although associated with less complications (approximately 1% vs. up to 16% [4]), the former may be less accurate than the latter. Furthermore, an open biopsy after an initial non-diagnostic CT-guided biopsy often implies a second general anaesthesia, especially in younger children. Moreover, this may cause a diagnostic delay. Nevertheless, a few studies have reported that CT-guided bone biopsy in pediatric patients is a safe procedure with comparable diagnostic yield to that in adults, and a valid alternative to direct open biopsy [5-7].

Although CT-guided biopsy is a promising method for the evaluation of bone lesions in pediatric patients, a problem arises when the acquired tissue is judged to be inadequate or inconclusive by the pathologist to establish a diagnosis. The final outcome of bone lesions with indeterminate CT-guided biopsy results (particularly in terms of malignant vs. benign nature) is important in determining the need for further diagnostic steps and patient counselling. Furthermore, a prior knowledge of which factors are associated with indeterminate CT-guided bone biopsy results is important, because patients with these characteristics may immediately be referred to open biopsy rather than initially undergoing a CT-guided biopsy to safe valuable time and avoid extra anaesthesia. Currently, there is very limited information on this topic in pediatric patients [6]. Although such data exist in adult populations [2, 3], they cannot be directly applied to pediatric patients, since the spectrum and epidemiology of bone lesions differs considerably between these two groups [8].

The aim of this study was therefore to determine the frequency of indeterminate percutaneous CT-guided bone biopsy in a pediatric population, the subsequent management of the indeterminant biopsy result, and the factors associated with indeterminate biopsy.

Materials and Methods

Study design and patients

This retrospective study was approved by the local institutional review board, and the requirement for informed consent was waived. The database of our university hospital (which is a tertiary referral center for bone tumors) was searched for all pediatric patients who underwent CT-guided bone biopsy between June 2008 and January 2017.

Inclusion criteria were: patients aged ≤21 years with a bone lesion of unknown nature and availability of a CT-guided biopsy of this bone lesion. CT-guided biopsy is performed for all bone lesions without any extraosseous soft tissue mass, and for all bone lesions with an extraosseous soft tissue mass that are too deeply located to be confidently visualized with ultrasonography. Exclusion criteria were: histopathological nature of the bone lesion already known before CT-guided biopsy, cancelled CT-guided biopsy, biopsy at the same time of radiofrequency ablation (RFA) of a known or clinically and radiologically suspected osteoid osteoma, spondylodiscitis, and bone lesions without a clear histopathological diagnosis that were treated (e.g., RFA, curettage and cavity filling, sclerosing therapy, radiation therapy)

Note that the decision to perform further tissue samplings after initial CT-guided biopsy was made for each individual patient by a multidisciplinary sarcoma panel and in consultation with the patient and parent(s). This decision depended on different factors, including history of malignancy, the presence of related symptoms, and imaging signs that may suggest malignancy (e.g. unsharp transition zone, aggressive periosteal reaction, cortical destruction, and associated soft tissue mass).

CT-guided biopsy

Each CT-guided biopsy was performed by one of five musculoskeletal radiologists (with a minimum of 2, 5, 7, 9, and 9 years of experience, respectively) as part of routine clinical care. Using a Siemens Somatom Sensation 16 or a Siemens Definition 64 AS CT-scanner (Erlangen, Germany), full-dose unenhanced CT images of the bone lesion were acquired for biopsy planning (just prior to biopsy) with tube voltage ranging between 80 and 140 kV (adjusted according to age, weight, and body region) and automatic dose modulation. This pre-biopsy planning CT-scan included the bone lesion of interest and surrounding normal appearing tissue.

All patients then underwent core needle biopsy under CT guidance with variable needle size (ranging between 8 and 18 gauge) and number of biopsy passes, at the discretion of the musculoskeletal radiologist. 8-gauge biopsy (Snarecoil, Ranfac, Avon, MA, USA), 11-gauge battery-powered biopsy (Arrow OnControl, Teleflex Inc, Morrisville, NC, USA), and 16- and 18-gauge biopsy (BioPince, Argon Medical Devices Inc, Athens, TX, USA) devices were used in this study.

Histopathological examination

The acquired bone biopsy specimens were evaluated by an expert musculoskeletal pathologist (with more than 25 years of experience) as part of routine clinical care. CT-guided bone biopsies were defined as diagnostic if they yielded a specific benign or malignant diagnosis, whereas CT-guided biopsies were defined as indeterminate if they yielded insufficient material for a specific diagnosis to be made or to suggest a malignancy.

CT image evaluation

Pre-biopsy planning CT-scans were independently reviewed by two radiologists (T.C.K. and Ö.K.) with 6 and 4 years of experience in musculoskeletal imaging, using a Picture Archiving and Communication System workstation (Carestream Vue PACS version 11.4.1.1102, Carestream Health, Inc, Rochester, NY, USA). The readers knew patient's age and gender, but were blinded to all other clinical information, all imaging reports, histopathological results, whether or not a repeated biopsy was performed, and all clinical and imaging follow-up. CT datasets were reviewed in bone window (level/width of 700/3000) and soft-tissue (level/width of 40/500) settings on reconstructed 2.0-mm axial, coronal, and sagittal images. All bone lesions were assessed for location, density (purely lytic, sclerotic, or mixed), absence or presence of a sclerotic rim, transition zone (sharp vs. unsharp), periosteal reaction, cortical destruction, associated extraosseous soft tissue mass, and maximum tumor diameter in the axial plane. The findings of the two observers were used to determine interobserver agreement, but only the findings of the first observer were used for all other analyses.

Reference standard

Bone lesions were classified as benign if histopathological examination of a tissue sample (obtained by either CT-guided, open biopsy, or resection) revealed a specific benign lesion. Bone lesions were classified as malignant if histopathological examination of a tissue sample (obtained by either CT-guided, open biopsy, or resection) revealed malignancy. If initial CT-guided biopsy suggested a specific benign lesion, but subsequent second CT-guided, open biopsy, or resection (if performed) revealed a malignant lesion, the lesion was classified as malignant. If histopathological examination of any tissue sample yielded no specific benign diagnosis or malignancy, the lesion was classified as benign if related symptoms (if present) completely disappeared with conservative treatment (including withdrawal of pain medication, if administered at all), or if the lesion remained stable or regressed in size with conservative treatment during a follow-up of at least one year. In all other cases, the nature of the bone lesion was classified as unclear.

Statistical analysis

The percentages of diagnostic and indeterminate CT-guided bone biopsies were calculated, along with 95% confidence intervals (CIs). The percentages of benign and indeterminate CT-guided bone biopsies that eventually proved to be malignant were also calculated. Furthermore, the following clinical and CT features of bone lesions were compared between indeterminate and diagnostic CT-guided bone biopsies, using the Fisher's exact test for binary data, the Mann-Whitney

U test for non-Gaussian continuous data, and the unpaired *t* test for Gaussian continuous data: age, gender, history of malignancy, presence of bone lesion related symptoms, presence of multiple bone lesions, CT features as described previously, maximum length of biopsy sample (single largest core), and number of biopsy passes. The same clinical and bone lesion CT features were also compared between malignant vs. benign or indeterminate CT-guided bone biopsy results. Kolmogorov-Smirnov tests were first used to check whether continuous variables in the different groups were normally distributed. Interobserver agreement with regard to CT evaluation was assessed using the unweighted kappa statistic for dichotomous scores (with $\kappa < 0.2$, $\kappa > 0.2$ to $\kappa \leq 0.4$, $\kappa > 0.4$ to $\kappa \leq 0.6$, $\kappa > 0.6$ to $\kappa \leq 0.8$, and $\kappa > 0.8$ to $\kappa \leq 1$ regarded as poor, fair, moderate, good, and very good agreement, respectively) and Bland-Altman analysis for maximum tumor size measurements (with calculation of mean absolute difference [bias] and 95% confidence interval of the mean difference [limits of agreement]). *P*-values <0.05 were considered statistically significant. Statistical analyses were executed using MedCalc version 17.2 Software (MedCalc, Mariakerke, Belgium).

Results

Patients and CT-guided bone biopsies

A total of 121 patients were potentially eligible for inclusion. Of these 121 patients, 27 were excluded because of biopsy at the same time of RFA of an already known or clinically and radiologically suspected osteoid osteoma, 4 patients were excluded because they had a bone lesion without a clear histopathological diagnosis that was treated with local therapy, 2 were excluded because the histopathological nature of the bone lesion was already known before CT-guided biopsy and RFA were performed at our institution (chondroblastoma and osteoblastoma), 1 patient was excluded because of spondylodiscitis, and 1 patient was excluded because CT-guided biopsy was cancelled due to safety concerns while the procedure was ongoing (it was decided that a bone lesion in the T8 vertebra could not be safely biopsied). Thus, 86 patients (mean age of 15.4 ± 5.2 years, age range of 1-21 years, 41 males and 45 females) were finally included. Eighty-three patients underwent CT-guided biopsy of 1 bone lesion, and 3 patients underwent CT-guided biopsy of 2 different bone lesions, yielding a total of 89 CT-guided bone biopsies. A flowchart with patient inclusion in this study is shown in **Figure 1**. The basic characteristics of included patients are shown in **Table 1**.

Diagnostic yield of CT-guided bone biopsies

CT-guided biopsy of 89 bone lesions was indeterminate in 29 cases (indeterminate proportion of 32.6% [95% CI: 23.7-42.9%]), and yielded a specific benign diagnosis

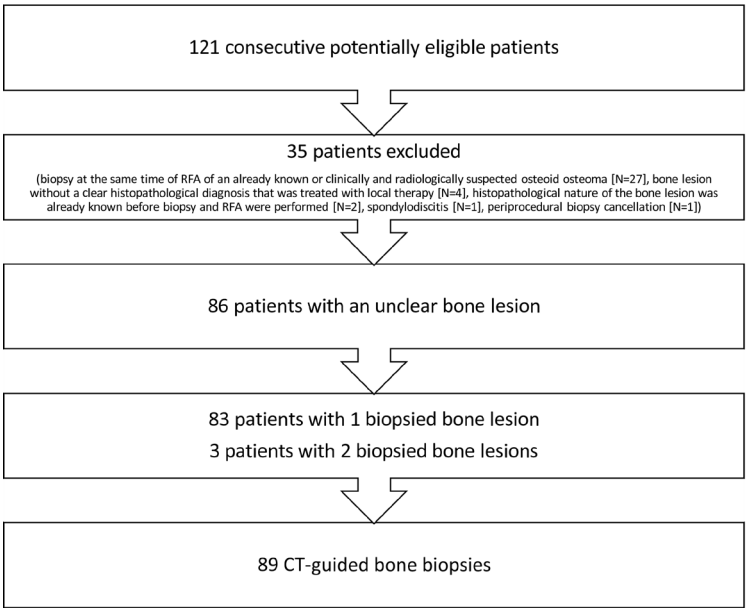

Figure 1. Flowchart showing patient inclusion in this study.

in 37 cases and a malignancy in 23 cases (diagnostic proportion of 67.4% [95% CI: 57.1-76.3%]). An overview with the outcome of the 89 CT-guided bone biopsies is shown in **Figure 2**. Of 29 non-diagnostic biopsies, 24 were signed out as indeterminate and 5 as "insufficient tissue for diagnosis" by pathology. Histopathological results of the 60 diagnostic CT-guided biopsies are shown in **Table 2**.

Indeterminate lesions on CT-guided biopsy

Fifteen of 29 lesions that were indeterminate on CT-guided biopsy did not undergo further tissue sampling, whereas 14 did (4 underwent a second CT-guided biopsy, 1 underwent a second CT-guided biopsy and subsequent resection, 4 underwent open biopsy, and 5 underwent resection). These additional tissue samplings did not lead to a specific diagnosis in 5 cases, whereas it led to a specific diagnosis in 9 cases (aneurysmal bone cyst [n=2], non-ossifying fibroma [n=2], chondroblastoma with secondary aneurysmal bone cyst [n=1], fibrous dysplasia [n=1], Langerhans cell histiocytosis [n=1], osteonecrosis [n=1], and Rosai-Dorfman disease [n=1]). Eighteen of 20 cases that were still without a clear histopathological diagnosis were eventually classified as benign, based on complete resolution of symptoms with conservative treatment during a median follow-up time of 21 months (range: 8-97 months) in 11 symptomatic lesions, and based on stability or regression in size

Table 1. Characteristics of included patients.

No. of patients	**86**
Age (years)	15.4 ± 5.2
Males/females	41 (47.7%) /45 (52.3%)
Known or history of malignancy or relevant bone disease	9/86 (10.5%)[a]
Presence of bone lesion(s) elsewhere	14/86 (16.3%)
No. of CT-guided bone biopsies	89[b]
Symptomatic bone lesion / indicentally found / unclear	71 (79.8%) / 10 (11.2%) / 8 (9.0%)
No. of bone lesions in anatomic sites	
-Femur	32 (36.0%)
-Tibia	14 (15.7%)
-Vertebra	9 (10.1%)
-Sacrum	6 (6.7%)
-Iliac bone	5 (5.6%)
-Fibula	4 (4.5%)
-Humerus	3 (3.4%)
-Acetabulum	3 (3.4%)
-Metatarsal bone	3 (3.4%)
-Clavicle	2 (2.2%)
-Pubic bone	2 (2.2%)
-Coracoid	1 (1.1%)
-Scapula	1 (1.1%)
-Radius	1 (1.1%)
-Sternum	1 (1.1%)
-Rib	1 (1.1%)
-Talus	1 (1.1%)
General / local anesthesia	31 (34.8%) / 58 (65.2%)
Median biopsy needle size with range (gauge)	11 (8-18)[c]
Median no. of biopsy passes with range	1 (1-6)[d]
Median maximum length biopsy sample with range (mm)	15 (4-40)[e]
Reported biopsy-related complications	None

Notes:
[a] Rhabdomyosarcoma (n=2), acute lymphoblastic leukemia (n=1), Burkitt lymphoma (n=1), Ewing sarcoma (n=1), follicular dendritic cell sarcoma (n=1), Hodgkin lymphoma (n=1), osteosarcoma (n=1), and synovial carcinoma (n=1)
[b] Three patients underwent CT-guided biopsy of 2 different bone lesions
[c] Biopsy needle size reported in 13/89 biopsies
[d] Number of biopsy passes reported in 84/89 biopsies
[e] Maximum length biopsy sample reported in 83/89 biopsies (in 5 cases only "small fragments" and in 1 case no related notes in the pathology report; these 6 cases were excluded)

with conservative treatment during a median follow-up time of 32 months (range: 13-70 months) in 7 lesions without (clear) related symptoms. In 2 cases, the lesions remained of indeterminate nature (one patient without (clear) related symptoms who had a follow-up time of only 9 months, and one patient with a symptomatic

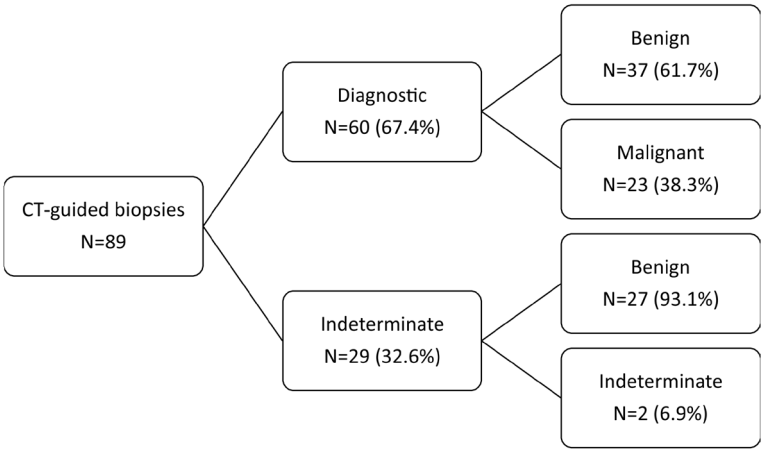

Figure 2. Outcome of 89 CT-guided bone biopsies.

Table 2. Histopathological results of 60 diagnostic CT-guided biopsies.

Specific benign diagnoses (n=37)	
-Giant cell tumor	7
-Aneurysmal` bone cyst	7
-Chondroblastoma	6
-Fibrous dysplasia	5
-Bacterial osteomyelitis	4
-Langerhans cell histiocytosis	2
-Non-ossifying fibroma	2
-Osteofibrous dysplasia-like adamantinoma	2
-Chondromyxoid fibroma	1
-Osteoblastoma	1
Malignancies (n=23)	
-Osteosarcoma	10
-Ewing sarcoma	5
-Acute lymphatic leukemia	3[a]
-Chondrosarcoma grade 1	3
-Metastasis embryonic rhabdomyosarcoma	1
-Metastasis follicular dendritic cell sarcoma	1

Notes:
[a] All 3 patients presented with normal blood counts and focal bone lesion(s)

lesion experienced less but not completely resolved pain with conservative treatment after 9 months follow-up). Excluding these 2 latter cases, no malignancy was eventually diagnosed in any of the remaining 27 cases that were indeterminate on initial CT-guided biopsy (0%; 95% CI: 0-12.5%). Representative cases are shown in **Figures. 3-6**.

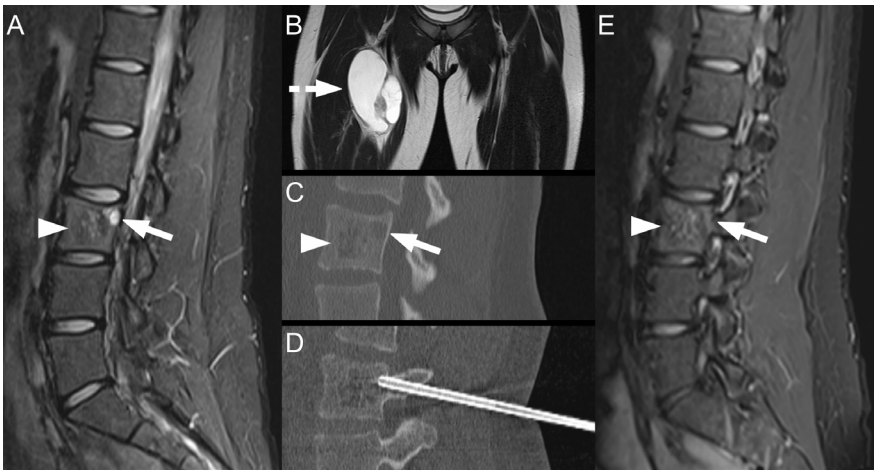

Figure 3. A 16-year-old girl presented with backache radiating to the right leg. MRI was ordered because of the suspicion of disc herniation. Sagittal fat-suppressed T2-weighted image showed an area compatible with hemangioma in the L3 vertebra (A, arrowhead), but also a second lesion of high signal intensity posterior in the L3 vertebra (A, arrow). There was no disc herniation. Of note, this patient was successfully treated for synovial carcinoma in the right rectus femoris muscle 4 years before. Coronal T2-weighted MRI that was performed at that time showed the synovial carcinoma with high signal intensity (B, dashed arrow), similar to the signal intensity of the lesion that was found posterior in the L3 vertebra (A, arrow). Because of the suspicion of metastatic synovial carcinoma, CT-guided biopsy was performed. Sagittal 2.0-mm pre-biopsy planning CT shows a faintly lytic 9-mm lesion posterior in L3 (C, arrow), with an unsharp transition zone, but no sclerotic rim, periosteal reaction, cortical destruction, or associated extraosseous soft tissue mass. The area compatible with hemangioma is also visible (C, arrowhead). Sagittal CT shows the tract of the biopsy needle just before tissue sampling was done (D). The acquired 28-mm tissue sample could neither establish a specific benign diagnosis, nor suggest malignancy. Sagittal fat-suppressed T2-weighted MRI that was performed 48 months later stilled showed the hemangioma (E, arrowhead), but there was complete resolution of the previously visible lesion posterior in L3 (E, arrow) without treatment. Therefore, this lesion without a clear histopathological diagnosis on CT-guided biopsy could eventually be classified as benign.

Benign lesions on CT-guided biopsy

Twenty-six of 37 benign lesions that were diagnosed by CT-guided biopsy did no undergo further tissue sampling, whereas 11 did (1 underwent open biopsy, 2 underwent open biopsy and resection, and 8 underwent resection). These additional tissue samplings did not change the diagnosis in 10 cases (giant cell tumor [n=3], chondroblastoma [n=2], osteofibrous dysplasia-like adamantinoma [n=2], aneurysmal bone cyst [n=1], chondromyxoid fibroma [n=1], and non-ossifying fibroma [n=1]), whereas it did in 1 case (diagnosis changed from aneurysmal bone cyst to giant cell tumor with secondary aneurysmal bone cyst). No malignancy was eventually diagnosed in any of the 26 cases that were benign on initial CT-guided biopsy (0%; 95% CI: 0-12.9%).

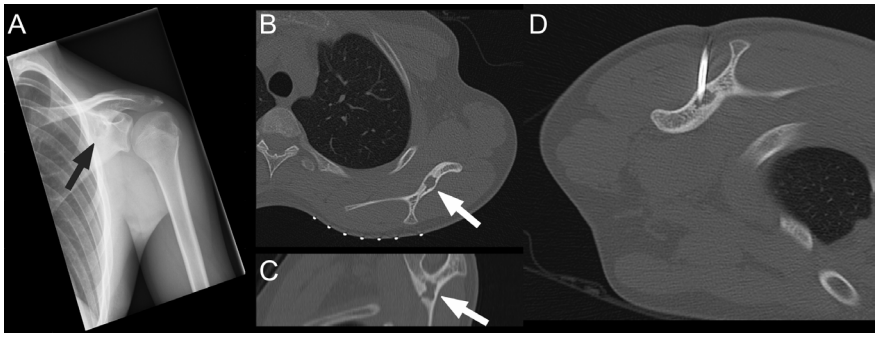

Figure 4. A 17-year-old boy presented with pain and some weakness around the left shoulder. Plain radiograph showed a lytic lesion in the left scapula (A, arrow). Of note, 7 years before, brain MRI (which was ordered because of central diabetes insipidus and growth hormone deficiency) showed an enhancing lesion in the infundibulum, which may have been due to extraosseous Langerhans cell histiocytosis (although not confirmed). Skeletal surveys did not reveal any bone lesions at that time. CT-guided bone biopsy of the lesion in the left scapula was performed. Axial and oblique coronal 2.0-mm pre-biopsy planning CT showed a lytic 11-mm lesion in the left scapula (C, arrow), with a sharp transition zone and focal cortical breakthrough, but no sclerotic rim, periosteal reaction, or associated extraosseous soft tissue mass. The acquired 4-mm tissue sample yielded insufficient material for a specific diagnosis to be made or to suggest a malignancy. However, the lesion proved to be Langerhans cell histiocytosis after subsequent resection.

Malignant lesions on CT-guided biopsy

Five of 23 malignancies that were diagnosed by CT-guided biopsy did not undergo further tissue sampling, whereas 18 underwent subsequent resection, which did not change the diagnosis in any of these cases (10 cases of osteosarcoma, 5 cases of Ewing sarcoma, and 3 cases of chondrosarcoma grade 1).

Clinical and CT features associated with indeterminate CT-guided bone biopsy results

Compared to patients with diagnostic CT-guided bone biopsies, patients with indeterminate bone biopsy results were significantly younger (median age of 14.0 vs. 18.0 years, *P*=0.0185), were more frequently female (72.4% vs. 41.7%, *P*=0.0007), and less frequently had bone lesion related symptoms (62.1% vs. 88.3%, *P*=0.0094). Furthermore, bone lesions were significantly more frequently invisible at CT (24.1% vs. 1.7%, *P*=0.0021), more frequently had a sclerotic rim (40.9% vs. 18.6%, *P*=0.0477), less frequently showed cortical destruction (45.5% vs. 72.9%, *P*=0.0343), less frequently had an associated extraosseous soft tissue mass (4.5% vs. 32.2%, *P*=0.0094), were smaller (median diameter of 17.0 vs. 31.0 mm, *P*=0.0007), and the maximum length of the biopsy sample was shorter (mean length of 10.9 vs. 17.8 mm, *P*=0.0003). History of malignancy, presence of multiple bone lesions, purely lytic bone lesion, sharp transition zone, periosteal reaction, and number of biopsy passes were not significantly different between diagnostic and indeterminate CT-guided bone biopsies. Corresponding results are summarized in **Table 3**.

Table 3. Clinical and CT features of bone lesions with indeterminate vs. diagnostic results on CT-guided bone biopsy.

Parameter	Indeterminate CT-guided bone biopsies	Diagnostic CT-guided bone biopsies	P-value (indeterminate vs. diagnostic CT-guided bone biopsies)
Age (years)	14.0[a] (9.5-18.0[b])	18.0[a,c] (14.5-19.0[b])	0.0185[d]
Gender (female)	21/29 (72.4%)	25/60 (41.7%)	0.0007[e]
History of malignancy	3/29 (10.3%)	6/60 (10.0%)	1.0000[e]
Symptoms related to bone lesion	18/29 (62.1%)	53/60 (88.3%)	0.0094[e]
Multiple bone lesions	7/29 (24.1%)	10/60 (16.7%)	0.4040[e]
Lesion invisible at CT	7/29 (24.1%)	1/60 (1.7%)	0.0021[e]
Purely lytic bone lesion[f]	17/22 (77.3%)	40/59 (67.8%)	0.5851[e]
Sclerotic rim[f]	9/22 (40.9%)	11/59 (18.6%)	0.0477[e]
Sharp transition zone[f]	15/22 (68.2%)	29/59 (49.2%)	0.1416[e]
Periosteal reaction[f]	2/22 (9.1%)	16/59 (27.1%)	0.1317[e]
Cortical destruction[f]	10/22 (45.5%)	43/59 (72.9%)	0.0343[e]
Extraosseous soft tissue mass[f]	1/22 (4.5%)	19/59 (32.2%)	0.0094[e]
Maximum tumor diameter (mm)[g]	17.0[a,c] (11.75-23.75[b])	31.0[a] (21.25-58.75[b])	0.0007[d]
Maximum length biopsy sample (mm)[j]	10.9[h] ± 5.7	17.8[h] ± 8.7	0.0003[i]
No. of biopsy passes[k]	1[a,c] (1-1[b])	1[a,c] (1-1[b])	0.2192[d]

Notes: [a] Median; [b] Interquartile range; [c] Not normally distributed according to Kolmogorov-Smirnov test ($P<0.05$); [d] Mann-Whitney U test; [e] Fisher's exact test; [f] Excluding 8 lesions that were lesions not visible at all at CT (only visible at MRI); [g] Excluding 8 lesions that were lesions not visible at all at CT (only visible at MRI) and 1 lesion that was not reliably measurable; [h] Mean; [i] Unpaired *t* test; [j] As assessed by the interpreting pathologist, excluding 6 missing data; [k] Excluding 5 missing data

Clinical and CT features associated with malignant CT-guided bone biopsy results

Compared to patients with CT-guided bone biopsies that yielded benign or indeterminate results, patients with CT-guided bone biopsies that yielded malignant results significantly more frequently had multiple bone lesions (39.1% vs. 12.1%, $P=0.0108$). Furthermore, bone lesions were significantly less frequently purely lytic (39.1% vs. 82.8%, $P=0.0003$), less frequently had a sclerotic rim (4.3% vs. 32.8%, $P=0.0087$), less frequently had a sharp transition zone (17.4% vs. 69.0%, $P=0.0000$), more frequently had a periosteal reaction (52.2% vs. 10.3%, $P=0.0000$), more frequently had an associated extraosseous soft tissue mass (65.2% vs. 8.6%, $P=0.0000$), were larger (median diameter of 56.4 vs. 27.2 mm, $P<0.001$), and were biopsied with significantly more biopsy passes ($P=0.0257$). Age, gender, history of malignancy, bone lesion related symptoms, presence of multiple bone lesions,

Table 4. Clinical and CT features of bone lesions with malignant results vs. those with benign or indeterminate results on CT-guided bone biopsy.

Parameter	CT-guided bone biopsies with malignant results	CT-guided bone biopsies with benign or indeterminate results	P-value (malignant vs. benign or indeterminate CT-guided bone biopsy results)
Age (years)	17.0[a] (14.0-19.0[b])	17.0[a,c] (12.0-19.0[b])	0.4366[d]
Gender (female)	8/23 (34.8%)	38/66 (57.6%)	0.0891[e]
History of malignancy	2/23 (8.7%)	7/66 (10.6%)	1.0000[e]
Symptoms related to bone lesion	21/23 (91.3%)	50/66 (75.8%)	0.1394[e]
Polyostotic	9/23 (39.1%)	8/66 (12.1%)	0.0108[e]
Lesion invisible at CT	0/23 (0%)	8/66 (12.1%)	0.1064[e]
Purely lytic bone lesion[f]	9/23 (39.1%)	48/58 (82.8%)	0.0003[e]
Sclerotic rim[f]	1/23 (4.3%)	19/58 (32.8%)	0.0087[e]
Sharp transition zone[f]	4/23 (17.4%)	40/58 (69.0%)	0.0000[e]
Periosteal reaction[f]	12/23 (52.2%)	6/58 (10.3%)	0.0000[e]
Cortical destruction[f]	19/23 (82.6%)	34/58 (58.6%)	0.0681[e]
Extraosseous soft tissue mass[f]	15/23 (65.2%)	5/58 (8.6%)	0.0000[e]
Maximum tumor diameter (mm)[g]	56.4[h] ± 27.8	27.2[h] ± 20.2	<0.001[i]
Maximum length biopsy sample (mm)[j]	16.0[a] (11.0-25.0[b])	12.0[a,c] (9.0-18.0[b])	0.1437[d]
No. of biopsy passes[k]	1[a,c] (1-3[b])	1[a,c] (1-1[b])	0.0257[d]

Notes: [a] Median; [b] Interquartile range; [c] Not normally distributed according to Kolmogorov-Smirnov test ($P<0.05$); [d] Mann-Whitney U test; [e] Fisher's exact test; [f] Excluding 8 lesions that were lesions not visible at all at CT (only visible at MRI); [g] Excluding 8 lesions that were lesions not visible at all at CT (only visible at MRI) and 1 lesion that was not reliably measurable; [h] Mean; [i] Unpaired *t* test; [j] As assessed by the interpreting pathologist, excluding 6 missing data; [k] Excluding 5 missing data

(in)visibility of the bone lesion at CT, cortical destruction, and maximum length of the biopsy sample were not significantly different between bone lesions with malignant results vs. those with benign or indeterminate results on CT-guided bone biopsy. Corresponding results are summarized in **Table 4**.

Interobserver agreement

Interobserver for the assessment of the presence of a purely sclerotic bone lesion, a sclerotic rim, sharp transition zone, periosteal reaction, cortical destruction, and extraosseous soft tissue mass was very good, with κ values of 1.0, 0.872, 0.849, 1.0, 0.877, and 1.0, respectively. Mean bias ± limits of agreement for maximum tumor diameter measurement was 1.1 ± 6.4 mm.

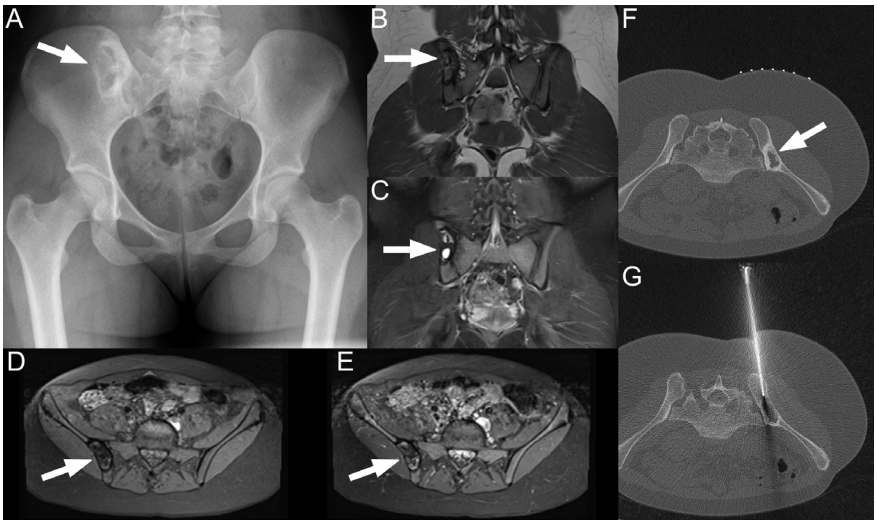

Figure 5. A 19-year-old girl without any relevant medical history presented with long lasting vague left-sided abdominal pain, for which a plain abdominal radiograph was ordered to assess for constipation. Although the radiograph did not show any signs of intestinal pathology, it revealed a lytic lesion with sclerotic margins in the right iliac wing (A, arrow). The lesion was asymptomatic. MRI with coronal T1-weighted (B), coronal fat-suppressed T2-weighted (C), axial fat-suppressed T1-weighted (D), and axial gadolinium-enhanced fat-suppressed T1-weighted (E) sequences showed the lesion to be predominantly T1 hypointense, heterogeneously T2 hyperintense, and with minimal enhancement after gadolinium administration (arrows). Axial 2.0-mm pre-biopsy planning CT showed a lytic 40-mm lesion in the right iliac wing (F, arrow), with a sharp transition zone and a sclerotic rim, but no periosteal reaction, cortical destruction, or associated extraosseous soft tissue mass. Axial CT shows the tract of the biopsy needle just before tissue sampling was done (G). The acquired 12-mm tissue sample yielded insufficient material for a specific diagnosis to be made or to suggest a malignancy. A second CT-guided biopsy was performed three weeks later, which revealed osteonecrosis without any other lesional tissue.

Discussion

The results of this study show that around one-third of CT-guided biopsies of unclear bone lesions in pediatric patients yields material that is judged as inadequate or inconclusive by the pathologist to establish a diagnosis. None of the 29 bone lesions that were indeterminate on initial CT-guided biopsy in this study proved to be malignant based on available subsequent tissue samplings and follow-up. Lower age, female gender, lack of symptoms related to the bone lesion, invisibility of the bone lesion at CT, the presence of a sclerotic rim, absence of cortical destruction, absence of an associated soft tissue mass, smaller tumor diameter, and a smaller biopsy sample length were (univariately) significantly associated with indeterminate CT-guided bone biopsy results.

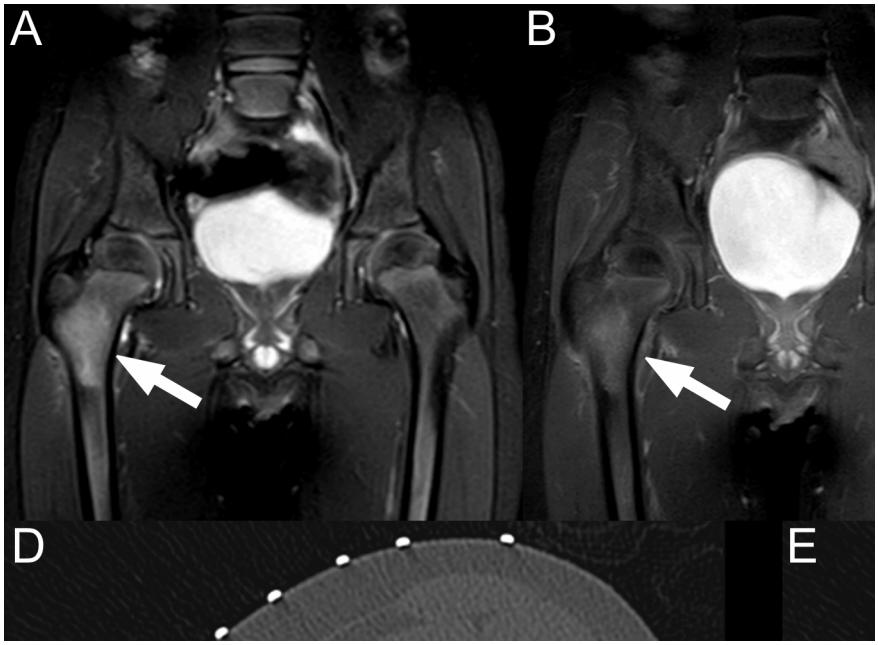

Figure 6. A 5-year-old boy without any relevant medical history presented with pain in the right hip and night sweats since one week. A conventional radiograph of the right hip (not shown) was unremarkable. Coronal fat-suppressed T2-weighted (A) and gadolinium-enhanced MRI (B) showed a T2 hyperintense and contrast-enhancing lesion in the proximal right femur (arrows) with some surrounding soft tissue induration. Coronal positron emission tomography (PET)/CT showed the lesion to be ^{18}F-fluoro-2-deoxy-D-glucose (FDG)-avid (C, arrow). There were no other FDG-avid lesions on whole-body PET/CT. The lesion is invisible on axial 2.0-mm pre-biopsy planning CT (D). Axial CT shows the tract of the biopsy (E). The acquired 4-mm tissue sample yielded insufficient material for a specific diagnosis to be made or to suggest a malignancy. All symptoms resolved with conservative treatment within one month, and the patient remained completely symptom-free at eight months follow-up. The lesion was therefore classified as benign.

Based on these results, it appears that indeterminate CT-guided bone biopsy results in children are relatively common and that it is unlikely that these bone lesions have a malignant nature. The latter finding is completely in line with the fact that several benign CT features and a smaller biopsy sample length (which occurs more frequently in benign lesions because they are often smaller with less soft tissue mass than malignant lesions) were significantly associated with indeterminate CT-guided bone biopsy results. However, the reasons for the positive relationship between lower age and female gender with indeterminate CT-guided bone biopsy results, as found in the present study, remain unclear.

The proportion of indeterminate CT-guided bone biopsies in the present study (32.6%) is higher than in a previous study by Hryhorczuk et al. [6] that evaluated 63 CT-guided bone biopsies in 61 children (mean age of 11.6 years, age range 6 weeks-18 years), which reported 14 indeterminate biopsy results (23.0%). The authors of that study described that at their institution, CT-guided biopsy of bone lesions in children is most often performed to confirm that an osseous lesion is benign, to assess for infection or to diagnose metastases or a primary musculoskeletal tumor [6]. In the present study, no biopsies were performed to confirm the benignity of a bone lesion if it was already suggested by clinical and radiological findings. This may explain the higher ratio of non-diagnostic results in the present series. Several other studies have evaluated the diagnostic yield of percutaneous image-guided biopsied of musculoskeletal lesions [5, 9-11], which reported non-diagnostic results varying between 15% and 29%. However, these studies either mixed both CT-guided and ultrasound-guided biopsies for both bone lesions and soft tissue lesions without bone involvement [5, 9, 11], or analyzed the yield of CT-guided bone biopsied for a mix of both bone lesions and soft tissue lesions without bone involvement [10]. Because of the inclusion of ultrasound-guided biopsies and soft tissue lesions without bone involvement in these studies, comparison with the present results is not very meaningful. Other studies only included bone lesions that were biopsied under CT guidance [2, 3], but these were not performed in a pediatric population. One of the largest studies on this topic by Hwang et al. [2] that included 800 mainly adult patients (with a median age of 60 years), reported initial CT-guided bone biopsy to be diagnostic in 69% and indeterminate in 31%, in line with the present results in pediatric patients. In the previously mentioned study by Hryhorczuk et al. [6] in children, 12 of the 14 patients with indeterminate CT-guided bone biopsy results underwent open biopsy, which did not show any signs of malignancy in 11 cases. In one case, open biopsy showed lymphoma, although it should be mentioned that the initial "indeterminate" CT-guided bone biopsy already suggested necrotic tumor suspicious for lymphoma [6]. The two other cases with indeterminate CT-guided bone biopsy results were not further reported on [6]. Despite its smaller sample size and lack of follow-up [6], the results of that study are in line with the results of the present study, in that indeterminate CT-guided bone biopsy results are relatively common but unlikely prove to be malignant. Interestingly, this observation is considerably different from that in adults. In the previously mentioned study by Hwang et al. [2], 154 bone lesions with initially indeterminate results, a malignant nature was eventually diagnosed in 39% [2]. These data reflect the considerable difference in the spectrum and epidemiology of bone lesions between pediatric and adult patients, and show that

indeterminate CT-guided bone biopsy results should be managed differently in pediatric patients.

The apparent very low risk of malignancy in pediatric patients with indeterminate CT-guided bone biopsy results is useful information for counselling patients and their parents, who may be stressed because of an unknown diagnosis, and who may worry about a possible underlying malignancy. Moreover, these data suggest that close imaging and clinical follow-up may be used instead of additional (open) biopsies in such patients. However, a crucial precondition is the availability of a team consisting of radiologists, pathologists, and clinicians with significant expertise in the management of pediatric bone tumors. It remains important to carefully review each individual case with a non-diagnostic CT-guided bone biopsy and to perform a repeat biopsy in a timely manner if there is any clinical or radiological suspicion for malignancy. The clinical and CT features of bone lesions that were associated with indeterminate CT-guided bone biopsy results (and which showed a very good interobserver agreement) may be helpful in multidisciplinary decision making whether or not a CT-guided bone biopsy can be useful, or if open biopsy or close imaging follow-up are more indicated. It should also be noted that dealing with malignancy or not is not the only matter, and that additional tissue samplings in these patients may still be useful to diagnose a specific benign diagnosis that can have clinical consequences (13 additional tissue samplings in 29 indeterminate CT-guided bone biopsy results yielded 9 specific benign diagnoses of which 5 with clinical consequences [2 aneurysmal bone cysts, 1 chondroblastoma with secondary aneurysmal bone cyst, 1 Langerhans cell histiocytosis, and 1 Rosai-Dorfman disease]).

This study had several limitations. First, its results were obtained in an institution with radiologists, pathologists and clinicians that have significant experience with pediatric bone tumors. These results may not be duplicated when the requisite experience is not available. Second, due to the retrospective design, variable imaging procedures were performed before CT-guided bone biopsy. Because of this inconsistency in previous imaging, only pre-biopsy planning CT-scans were evaluated. Third, due to missing data, the association of biopsy needle size and the use of manual or battery-powered bone drill systems with indeterminate CT-guided bone biopsy results could not be assessed. Fourth, because five different musculoskeletal radiologists performed all 89 biopsies over a period of 8.5 years, the effect of experience and operator dependence on diagnostic yield could not be assessed either. Fifth, although 86 patients with 89 CT-guided bone biopsies were included, the number was too low to perform a multivariate logistic regression analysis to determine which clinical and CT features of bone lesions

were independently associated with indeterminate CT-guided bone biopsy results. Sixth, 2 of 29 indeterminate lesions on CT-guided biopsy could not be definitely classified as benign, and were excluded from analysis.

In conclusion, a non-diagnostic CT-guided biopsy result in a child with an unclear bone lesion suggests benignity. Several clinical and CT features of bone lesions are associated with indeterminate CT-guided bone biopsy results

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